Vascular Endothelial Growth Factor (VEGF) Bioavailability Regulates Angiogenesis and Intestinal Stem and Progenitor Cell Proliferation during Postnatal Small Intestinal Development.

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Authors: Christopher R Schlieve, Salvador Garcia Mojica, Kathleen A Holoyda, Xiaogang Hou, Kathryn L Fowler, Tracy C Grikscheit

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Public Summary:
Vascular endothelial growth factor (VEGF) is a highly conserved, master regulatory molecule required for endothelial cell proliferation, organization, migration and branching morphogenesis. Podocoryne carnea and drosophila, which lack endothelial cells and a vascular system, express VEGF homologs, indicating potential roles beyond angiogenesis and vasculogenesis. The role of VEGF in the development and homeostasis of the postnatal small intestine is unknown. We hypothesized regulating VEGF bioavailability in the postnatal small intestine would exhibit effects beyond the vasculature and influence epithelial cell stem/progenitor populations. METHODS: VEGF mutant mice were created that overexpressed VEGF in the brush border of epithelium via the villin promotor following doxycycline treatment. To decrease VEGF bioavailability, sFlt-1 mutant mice were generated that overexpressed the soluble VEGF receptor sFlt-1 upon doxycycline administration in the intestinal epithelium. Mice were analyzed after 21 days of doxycycline administration. RESULTS: Increased VEGF expression was confirmed by RT-qPCR and ELISA in the intestine of the VEGF mutants compared to littermates. The VEGF mutant duodenum demonstrated increased angiogenesis and vascular leak as compared to littermate controls. The VEGF mutant duodenum revealed taller villi and increased Ki-67-positive cells in the transit-amplifying zone with reduced Lgr5 expression. The duodenum of sFlt-1 mutants revealed shorter villi and longer crypts with reduced proliferation in the transit-amplifying zone, reduced expression of Dll1, Bmp4 and VE-cadherin, and increased expression of Sox9 and EphB2. CONCLUSIONS: Manipulating VEGF bioavailability leads to profound effects on not only the intestinal vasculature, but epithelial stem and progenitor cells in the intestinal crypt. Elucidation of the crosstalk between VEGF signaling in the vasculature, mesenchyme and epithelial stem/progenitor cell populations may direct future cell therapies for intestinal dysfunction or disease.

Scientific Abstract:
BACKGROUND: Vascular endothelial growth factor (VEGF) is a highly conserved, master regulatory molecule required for endothelial cell proliferation, organization, migration and branching morphogenesis. Podocoryne carnea and drosophila, which lack endothelial cells and a vascular system, express VEGF homologs, indicating potential roles beyond angiogenesis and vasculogenesis. The role of VEGF in the development and homeostasis of the postnatal small intestine is unknown. We hypothesized regulating VEGF bioavailability in the postnatal small intestine would exhibit effects beyond the vasculature and influence epithelial cell stem/progenitor populations. METHODS: VEGF mutant mice were created that overexpressed VEGF in the brush border of epithelium via the villin promotor following doxycycline treatment. To decrease VEGF bioavailability, sFlt-1 mutant mice were generated that overexpressed the soluble VEGF receptor sFlt-1 upon doxycycline administration in the intestinal epithelium. Mice were analyzed after 21 days of doxycycline administration. RESULTS: Increased VEGF expression was confirmed by RT-qPCR and ELISA in the intestine of the VEGF mutants compared to littermates. The VEGF mutant duodenum demonstrated increased angiogenesis and vascular leak as compared to littermate controls. The VEGF mutant duodenum revealed taller villi and increased Ki-67-positive cells in the transit-amplifying zone with reduced Lgr5 expression. The duodenum of sFlt-1 mutants revealed shorter villi and longer crypts with reduced proliferation in the transit-amplifying zone, reduced expression of Dll1, Bmp4 and VE-cadherin, and increased expression of Sox9 and EphB2. CONCLUSIONS: Manipulating VEGF bioavailability leads to profound effects on not only the intestinal vasculature, but epithelial stem and progenitor cells in the intestinal crypt. Elucidation of the crosstalk between VEGF signaling in the vasculature, mesenchyme and epithelial stem/progenitor cell populations may direct future cell therapies for intestinal dysfunction or disease.